REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-78, 79-97 and 110-115 were cancelled previously. Claims 98, 99 and 100 have been cancelled herein and rewritten as new claims 116, 117 and 118, respectively. Claims 101, 102 and 103 have been amended. Claims 101 through 109 and 116-118 are in the case and are before the Examiner.

I. The Amendments

Claims 99-101 have been cancelled and rewritten as independent claims using the limitations of the underlying previously recited base claim as the basis for each new independent claim. In addition, those claims have been amended to be in concert with the claims of co-pending divisional co-application Serial No. 10/806,006.

Thus, sub-paragraph (a) of claim 1 that was incorporated into claim 116 has been amended to clarify that one or more heterologous epitopes are present at the N-terminus or in the HBc immunogenic loop. Specific support for this amendment can be found at least in the paragraph bridging pages 7 and 8, page 22, middle paragraph, and each of the first full paragraphs of pages 26 and 27. The phrase "or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues," has also been cancelled from sub-paragraph (a) of claim the claim 1 recitation to maintain internal consistency within the new claim.

Sub-paragraph (c) has been of original claim 1 amended to recite that a sequence containing zero to about 100 amino acid residues can be present that is C-terminal to the HBc sequence that is "heterologous" to HBc. Particular support is found throughout the specification and in claims 18 and 42. This sub-paragraph of original claim 1 has also been revised to clarify that the "residues from position 135 to the HBc terminus" are HBc residues 136-140 by insertion of the phrase "through position 140 toward" after "position 135" with cancellation of the word "to". Support in the specification can be found in several places including at least at page 25, second sentence of the second paragraph; page 39, third sentence of the bridging paragraph; and page 44, first sentence of the bridging paragraph with page 45.

Sub-paragraph (d) of claim 117 has been amended relative to claim 18 to recite that Domain IV contains "5 through fourteen" residues from position 136 through position 149. Specific support can again be found through out the specification, but particularly in original claims 42, 78 and 82.

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112, Second Paragraph

The Action has a number of rejections based on the second paragraph of Section 112, and those rejections will be

dealt with hereinafter in the order that they were raised in the Action.

(1) Incomplete claims

The base claims for each of the application's claims were claimed prior to the present Action. The claims have been amended by reciting the remainder of each of the recited underlying base claims, as those or similar claims were amended in a recent Reply to a divisional application. It is thus believed that this basis for rejection is moot.

(2) "Variant, analog or complement thereof"

Claims 98 through 109 were rejected as allegedly indefinite for their use of one or more of the phrases "variant, analog or complement thereof". The Action asserts that the terms are "relative … which renders the claim indefinite". The Action asserts that the terms are not defined by the claims and that "the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." This basis for rejection cannot be agreed with and is respectfully traversed.

It should be quite apparent to anyone of ordinary skill in the art as to what a complementary sequence is, inasmuch as such sequences form the double helices of DNA. It is therefore presumed that the Examiner does not seek a further definition for that phrase. The other two phrases are defined at least in the paragraph bridging pages 55 and 56 and continuing through the paragraph that bridges pages 56 and 57.

As such, it is believed that this basis for rejection is moot and should be withdrawn.

B. Rejection Under 35 USC §112, First Paragraph

The pending claims were rejected under the first paragraph of Section 112 as allegedly being non-enabling in regard to certain aspects of the recitations regarding the C-terminal portion of the HBc portion of a sequence of the chimer. It is believed that these bases for rejection have been made moot by the previously discussed amendments, so no more is thought necessary to be said here.

C. Rejections Under 35 USC §102(b)

(1). Zlotnick et al.

The pending claims were rejected as allegedly anticipated by the teachings of the paper by Zlotnick et al. (hereinafter Zlotnick) that was document A29 of the IDS. This rejection is respectfully traversed as discussed below.

The Action has tried to characterize the Zlotnick disclosures in terms of the present claims, and has failed to appreciate what it is that Zlotnick has disclosed. The Action has also used a non-technical dictionary to try to find a meaning instead of relying on the document itself, an action a skilled worker would not do.

Zlotnick made three HBc-like sequences. Those materials are shown schematically in Fig. 1a at the top of page

9557. From the top down, the first is native HBc that was made by other than Zlotnick. The next construct, identified as Cp149, was C-terminally truncated to position 149 and contained the cysteines at their native positions of 48, 61 and 107. The second "new" construct is identified as Cp*149 that contains an alanine, "A", in place of each of the above-noted cysteines, and was similarly C-terminally truncated. The third "new" construct was denominated Cp*150. That construct was similarly C-terminally truncated and had the same three alanines replacing the three internal cysteines, as well as an added cysteine at residue position 150. The last construct included the protamine sequence from position 150 through position 183 and is not germane to this discussion.

Thus, only construct Cp*150 contained a C-terminal cysteine, but that structure had non-conservative substitutions of alanine for cysteine, and neither an added linker for an epitope, an epitope at the N-terminus or in the immunogenic loop. Thus, none of the Zlotnick structures anticipates what is claimed here.

The properties of that Zlotnick construct provide no insight nor suggestion about another construct, such as that claimed herein that contains an inserted peptide-bonded epitope sequence. Indeed, the Schödel papers discussed in the paragraph bridging pages 6 and 7 of the specification note the instability observed with C-terminally-truncated HBc proteins that contain insertions in their sequences as is claimed herein. Thus, the import of the heterologous residues whose presence is neither shown nor suggested by Zlotnick is that such residues are known in the art to cause instability.

As noted previously, the art knew that HBc with its otherwise native linker residues was a poor bonder with added antigens so there was an art-recognized need for additional linker residues. To proclaim that other residues are available to serve a linker function only admits a lack of ordinary knowledge in this field. This basis for rejection should be withdrawn.

2. Yoshikawa et al.

The pending claims were also rejected as allegedly anticipated by the disclosures of the paper by Yoshikawa et al., (1993) *J. Virol.* **67(10):**6064-6070 (hereinafter Yoshikawa). The Yoshikawa teachings also fail to anticipate the presently claimed invention as none of the constructs disclosed in that paper contain a peptide-bonded epitope sequence at the N-terminus of the HBc sequence nor inserted in the immunogenic loop. The sequence of construct pHBCx0 shown schematically at the top of Fig. 1 of that paper contains an added Cys residue as an artifact of the multiple cloning site added to the DNA that encodes the C-terminus of the molecule, but again lacks an added N-terminal or loop-inserted epitope sequence.

The Action cited a paper to Bukh et al. for the proposition that the added HCV sequences shown in Yoshikawa's Fig. 1 constructs pHBCx1-4 contained a Cys residue at position 173 from the N-terminus or that sequence. Taking the Action at its word, the presence of such a Cys neither anticipates the claims nor suggests these claims as the added HCV sequence that contains such a Cys is 180 residues in length and the claims recite a sequence heterologous to HBc that is about 100 residues

in length. Thus, this paper should also be withdrawn as a reference against the claims.

D. Rejection Under 35 USC §103(a)

Claims 98-109 were rejected as allegedly obvious over the disclosures of IDS document A16 by Pumpens et al. [(1995) *Intervirology*, **38**:63-74] hereinafter Pumpens, in view of Zlotnick, noted previously. This rejection is respectfully traversed.

The Action noted that Pumpens states that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." That statement was echoed by the later-published Borisova paper of Exhibit 1 [Borisova et al., *Intervirology* **39**:16-22 (1996)] that states near the top of the right-hand column of page 18 "HBcΔ (C-terminally-truncated HBc particles) were less stable than the corresponding full-length protein particles."

The Action also noted that Pumpens asserted that foreign insertions internal to the sequence "also exert an stabilizing effect on chimeric HBCΔ (sic) derivatives." The Action left out the basis for that statement, which was a parenthesized citation to unpublished results of Borisova. Interestingly, the Borisova paper of Exhibit 1 was published after the Pumpens paper and dealt with such internal insertions into HBc, but reported no enhancement of stability. Thus, Borisova had an opportunity to report on the alleged enhanced

stability and did not do so. That tends to negate the comment from unpublished results.

On the other hand, the present inventor asserts a lessening of stability with truncated HBc chimers that contain inserts that lack a C-terminal cysteine. His application has actual data in the examples that illustrate that instability, and further illustrate added stability for an otherwise identical chimer when a C-terminal cysteine is present. One skilled in the art would favor real data over a reference to unpublished results, particularly in view of the fact that the cited author of those unpublished results published on the underlying technology and made no mention of the alleged result.

The Action asserts that Zlotnick teaches that addition of a cysteine provided a stabilizing effect with two page citations. Thus, Zlotnick teaches in the Summary at page 9556 that addition of gold particles to an engineered mutant assembly domain provided a labeled protein unimpaired in its ability to form capsids. This construct was described in the text near the bottom of the right hand column of page 9556 just above "MATERIALS AND METHODS" was noted to have the three internal cysteines replaced by alanines and a new cysteine added at position 150. That construct was also referenced to Fig. 1a, as discussed previously.

The disclosure at page 9558 was somewhat more expansive, but still lacking as it was applied to the present claims. There, the same internal cysteine-lacking protein construct (Cp*150) with and with out gold was said to form capsids. The oxidized form of the cysteines was said to form oxidized disulfide-bonded dimers and the disulfides so formed

stabilize the quaternary structure of the capsids. Of course, that comparison was made with the Cp*149 construct that had no cysteines at all. However, this disclosure says nothing about the effect of a C-terminal cysteine on a truncated HBc molecule that has its internal cysteines nor such a molecule that has an inserted sequence.

The Action concluded that a worker of ordinary skill would be motivated to combine the above teachings to arrive at the claimed subject matter. This conclusion also cannot be agreed with, even if the relied-on disclosures were as stated. Because the disclosures have been so misconstrued and misstated, the conclusion reached in the Action is still further from propriety. As was already noted, the sidebar assertion of Pumpens upon which so much weight is placed that sequence insertions cause HBc chimer particle stabilization is unsubstantiated by the one to whom it was ascribed, Borisova, who had the opportunity and said nothing when he published thereafter on the same technology. Those assertions are further undermined by the sworn real data of the application that show a completely contrary result.

If one believed the unsubstantiated assertion of Pumpens, there would be no reason to add the C-terminal cysteines of Zlotnick by combining those teachings. Contrarily, if Pumpens were correct, the problem of instability would have been solved by inserting foreign sequences. Of course, had the instability problem been solved as suggested by the Action or as suggested by Pumpens, the problem alluded to in the application at page 7 and noted in Ulrich et al., *Adv. Virus Res.*, vol.50 (1998) Academic Press pages 141-182 (IDS document A28),

concerning "the requirement of reproducible preparation of intact chimer particles that can also withstand long-term storage" would have been met and Ulrich, writing three years after Pumpens, would have been mistaken.

Alternatively, if the skilled worker to whom this application is directed followed the usual procedure exhibited by workers of ordinary skill in science, and gave more credence to the later-published article of Ulrich over the earlier-published article of Pumpens that is cited in Ulrich, that worker would know that the problem of stability was not solved by inserting a heterologous sequence into the HBc sequence. Ulrich also cited the relied-on Zlotnick publication, and not having the present invention laid out before him did not suggest that stability could be achieved by combining those teachings. It is again submitted that this basis for rejection should be withdrawn.

E. Provisional Double-Patenting Rejection

Claims 98-109 (exclusive of cancelled claims) were provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting in view of specified claims of co-pending application No. 10/732,862. It is noted that the enumerated application has no allowed claims at this time. However, to speed prosecution, a Terminal Disclaimer and its appropriate fee are enclosed over the recited application.

F. Inventorship Issue

Dr. David R. Milich has asserted that he is a co-inventor of the present application and of application Serial No. 09/931,325. Counsel reviewed the matter and could not find a basis for naming Dr. Milich a co-inventor.

The undersigned hired an outside attorney, Mr. Talivaldis Cepuritis, to examine the matter both on behalf of Apovia, the assignee, and The Scripps Research Institute, Dr. Milich's employer at the time the present invention was made, to independently re-examine the matter. Mr. Cepuritis traveled from Chicago to San Diego and interviewed Drs. Birkett, Milich and G.B. Thornton, the Managing Director of Apovia, provided an opinion to Mr. Fitting for Scripps, the undersigned for Apovia and to Dr. Milich's counsel, Ms. Hamdan. Mr. Cepuritis found that Dr. Milich did not qualify as an inventor of either application. A copy of Mr. Cepuritis' Letter of Opinion is attached hereto as Exhibit 2, with its Appendix being Exhibits 2A and 2B.

F. New Art

Dr. Milich brought a new disclosure to the attention of counsel. That paper is provided herewith as Exhibit 3, and is noted on the enclosed Form PTO 1449. That paper is Chang et al. (1994) *J. Virol.*, **68(8):**5225-5231, hereinafter Chang. That Chang paper discloses several HBV constructs including full-length constructs and constructs C-terminally-truncated after HBc position 157 that also include the C-terminal two residues of HBc. That truncated construct is referred to as Δ157. Further constructs contained an inserted sequence from hepatitis

B surface antigen inserted between residues 78 and 80. That latter construct is referred to as Δ157L. The paper also discloses mixed constructs made from HBc molecules from different mammals.

The Chang constructs going so far into the C-terminal region of HBc would of necessity not be "self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell". As such, this disclosure does little for the skilled worker.

G. Priority

The Action noted that a Petition to correct the priority claim is needed. It is respectfully submitted that such a petition is not needed as is discussed below.

The subject application is one of two divisional applications that arose from US application Serial No. 09/930,915, that itself was a continuation-in-part of two provisional applications. The fact of this application's being a divisional application is noted on page 1 of the Application Data Sheet and also on the Utility Patent Application Transmittal sheet that was filed with the present application. Page 4 of the Application Data Sheet stated that the application was a continuation-in-part. The Preliminary Amendment that was filed along with the present application also amended the application to reflect the fact that this application is a divisional application as noted in 37 CFR § 1.78(a)(2)(iii). Thus, from the totality of the circumstances, the claim for priority was made timely, and no petition is needed.

The undersigned discussed this matter with a representative from the Patent Office OPLA who directed him to the USPTO web site and the a page directed to questions and answers regarding the eighteen-month Publication Questions and Answers. She particularly noted question CX6 and its answer that indicate that so long as the benefit claim was made in a timely manner a petition and its fee are not needed. A copy of the page bearing that question and answer are attached for the Examiner's convenience as Exhibit 4.

H. Summary

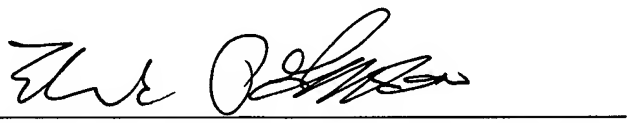
Claims 98, 99 and 100 were cancelled and rewritten as new claims 116, 117 and 118, respectively. Claims 101, 102 and 103 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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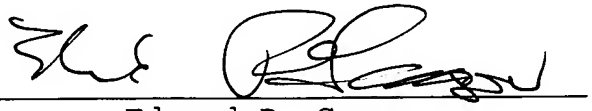
Enclosures
- Exhibits 1 through 4
- Petition and fee
- Terminal Disclaimer and fee
- PTO Form 1449

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on March 29, 2005.

By 
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